In Hypoparathyroidism

CALCIUM CONTROL ≠ DISEASE CONTROL

take
a closer
look

Hypoparathyroidism–A PTH Deficiency Disorder

Hypoparathyroidism is a rare and complex endocrine disorder characterized by absent or inappropriately low levels of endogenous parathyroid hormone (PTH).[1-3]

The critical role of PTH

PTH is an 84-amino-acid single-chain peptide secreted by the parathyroid glands in response to decreases in circulating ionized calcium.[1]

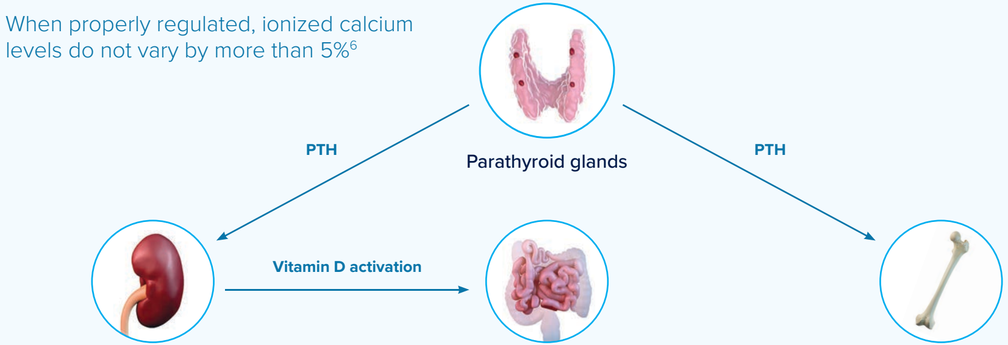
— Calcium, as well as magnesium, bind to calcium-sensing receptors on the glands to signal the synthesis and secretion of PTH

PTH works as a key regulator of mineral homeostasis, affecting several organ systems throughout the body.[1-3]

— Under normal, homeostatic conditions, these minerals are maintained within narrow ranges[4]

Normal mineral homeostasis with PTH[1-3,5]

When properly regulated, ionized calcium levels do not vary by more than 5%[6]



Diagnosing chronic hypoparathyroidism

Hypoparathyroidism occurs most frequently after inadvertent damage to the parathyroid glands during thyroidectomy, parathyroidectomy, or other neck surgeries.[7-9]

— In many cases, postsurgical hypoparathyroidism resolves within 6 months of surgery. However, if undetectable or inappropriately low levels of endogenous PTH persist for ≥6 months, a diagnosis of chronic hypoparathyroidism can be made

Impaired mineral homeostasis

Compromised PTH function leads to impaired mineral homeostasis throughout the body, often resulting in[1-3]:

Clinical Manifestations of Hypoparathyroidism

Symptoms may occur independent of mineral levels

Hypoparathyroidism can lead to a broad spectrum of clinical manifestations—ranging from mild to life-threatening, such as seizures, heart failure, or laryngospasm. A patient's clinical presentation is largely determined by the severity and rate of development of mineral imbalance, as well as disease duration.[2]

Patients may be...

Asymptomatic
despite having hypocalcemia and/or hyperphosphatemia[10]

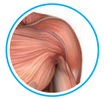
Symptomatic
despite being in the target serum calcium range[11,12]

take a closer look

Due to the variability in symptom presentation, careful and frequent monitoring is critical when evaluating patients with hypoparathyroidism.[8-10]

Signs and symptoms

For most patients, hypoparathyroidism initially presents with mild, nonspecific signs and symptoms associated with changes in mineral homeostasis. Below are common signs and symptoms patients may experience.[8,10]



Neuromuscular

- Fatigue
- Generalized muscle weakness
- Muscle cramping (sometimes painful), manifested as carpal and/or pedal spasm
- Neuromuscular irritability resulting in tetany
- Bronchospasm and wheezing

Neurologic

- Paresthesia and numbness, especially around the mouth and in the fingers and toes
- Seizures, spells
- Basal ganglia and brain calcifications

Neuropsychiatric

- Poor memory and concentration
- Depression
- Anxiety
- Personality disturbances

Cardiovascular

- Congestive heart failure, including cardiomegaly, pulmonary congestion, and volume overload
- Chest pain
- Arrhythmias
- Heart block
- Prolonged QTc interval

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It is important to **be alert and listen** for all potential disease developments, as patients may not attribute their symptoms with hypoparathyroidism.

Renal

A long-term follow-up study of 120 patients with hypoparathyroidism observed the following rates of renal complications[12]:

Hypercalciuria[a]

38%
(20/53)

of patients had hypercalciuria, defined as 24-hour urinary calcium >300 mg[12]

Nephrocalcinosis[a,b]

31%
(17/54)

of patients had intrarenal calcifications, including kidney stones and nephrocalcinosis[12]

Similar results were found in a recent prospective study of 90 patients with postsurgical hypoparathyroidism[13]:

- Patients had significantly higher rates of renal stones compared with controls (30% (27/90) vs 5% (7/142); *P*<0.001)

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Prolonged elevations in urinary calcium can contribute to several renal complications, including calcifications and impaired renal function.[1]

[a]Mitchell DM et al. A longitudinal retrospective cohort of 120 patients with hypoparathyroidism of diverse etiologies treated within a single tertiary-care hospital system. Chart reviews were performed and patients' biochemical parameters and rates of complications, including symptomatic hypocalcemia, hypercalciuria, and renal disease, were described.[12]

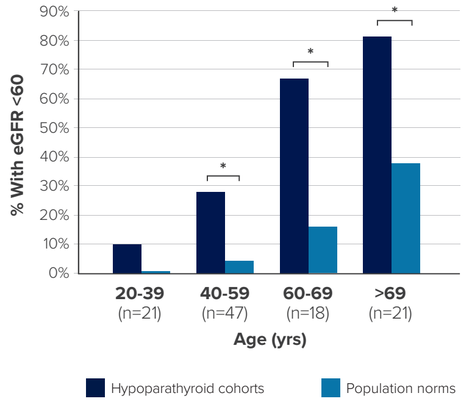
[b]Meola A et al. A prospective study of 90 patients with postsurgical hypoparathyroidism and 142 controls at an endocrine clinic. Biochemical parameters, such as serum calcium, phosphate, vitamin D, and urinary calcium, were used to assess for disease control, as well as renal ultrasound to screen for renal calcifications.[13]

Chronic kidney disease[a]

41%
(44/107)

of patients had eGFR <60 mL/min/1.73 m^2, consistent with CKD stage 3 or greater[12]

Compared with age-matched controls, these rates were **2 to 17x greater** in patients with hypoparathyroidism[12]

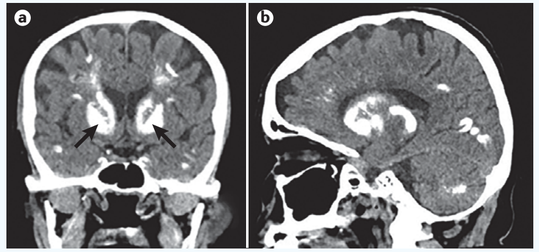


Proportion of patients with eGFR <60 mL/min/1.73 m^2 by age group.
*P<0.001 for comparison by one-sample t test.

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

Central Nervous System

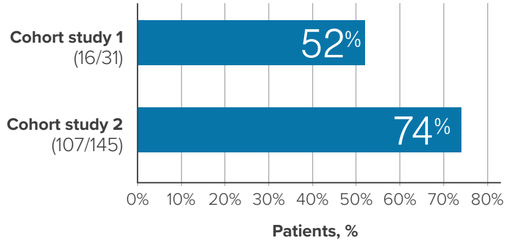
Basal ganglia calcifications[a,c]



Coronal (part **a**) and sagittal (part **b**) CT images of the head of an individual with hypoparathyroidism show extensive symmetrical calcifications involving the subcortical white matter, basal ganglia (arrows) and cerebellar hemispheres.[1]

Intracerebral calcifications, particularly in the basal ganglia, are often found in patients with hypoparathyroidism.

Observed rates of basal ganglia calcifications[12,14]



The clinical relevance of these calcifications is unclear.[1]

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Elevations in calcium phosphate product can lead to the deposition of insoluble mineral complexes in soft tissue.[8]

CT, computed tomography.

[c]Goswami R et al. An analysis of 145 patients with chronic idiopathic hypoparathyroidism. Repeat CT scans were performed to evaluate patients for the presence, volume, and progression of basal ganglia and other intracerebral calcifications.[14]

Neuropsychiatric comorbidities and disturbances[d]

Results from a survey of 397 patients with chronic hypoparathyroidism found that **nearly 30% (n=114)** were also diagnosed with a mental, behavioral, or neurodevelopmental disorder.[15]

In addition, patients reported experiencing the following symptoms as moderate to very severe:

47%
(n=186)
Slow or confused thinking

46%
(n=183)
Anxiety

41%
(n=161)
Sadness or depression

[d]Siggelkow H et al. A global patient and caregiver survey of 398 patients with hypoparathyroidism who self-identified as not adequately controlled with standard therapy and their caregivers. Health-related quality of life, health status, and hypoparathyroidism-associated symptoms were assessed to describe the overall burden of illness in hypoparathyroidism.[15]

Cardiovascular

Risk of CVD[e]

Several case-controlled analyses have evaluated the risk of CVD in patients with hypoparathyroidism from a Danish Patient Registry. These studies yielded conflicting results, with nonsurgical patients having an increased risk and postsurgical patients having no increased risk.[16,17]

However, a subsequent analysis of 459 patients, the majority of whom were postsurgical, identified several risk factors associated with an increased risk of CVD.[18]

RISK FACTOR	OR (95% CI)
Hypercalcemic events (≥4 events)	9.69 (2.63-35.79)
Severe hypocalcemia	3.01 (1.03-8.82)
Disease duration	3.67 (1.11-12.05)

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Fluctuations in serum calcium may have an impact on the risk of developing cardiovascular complications.[18]

CVD, cardiovascular disease; OR, odds ratio.

[e]Underbjerg L et al (2018). A case-controlled study of 459 patients with chronic hypoparathyroidism, the majority of which were postsurgical (n=380). This study assessed associations between biochemical findings and the risk of different long-term complications.[18]

Skeletal

Prolonged remodeling cycles[f]

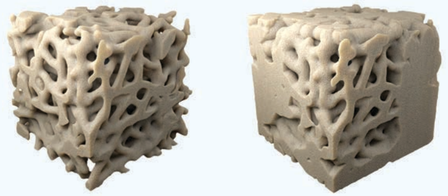
A histomorphometric analysis found that, when compared with controls, patients with hypoparathyroidism had[19]:

- Reduced remodeling rates and prolonged resorption period ($P<0.001$)
- Decreased bone formation surface and bone formation rate ($P<0.001$)

Abnormal bone microarchitecture[g]

Using 3-D micro-CT, a study observed several differences in cancellous bone structure between patients with hypoparathyroidism and age-matched controls[20]:

- Greater bone surface density ($P=0.04$)
- Increased trabecular thickness, trabecular number, and connectivity density ($P=0.04$, 0.05, 0.04, respectively)



Normal **Hypoparathyroidism**

take a closer look

Deficient PTH may lead to an increase in bone mineral density and structural changes to the bone.[1,3]

[f]Langdahl BL et al. A histomorphometric analysis of bone remodeling in 12 patients with hypoparathyroidism. Bone biopsies were obtained from each patient and bone structure parameters were evaluated, such as resorption phase length, resorption rate, bone formation surface and rate.[19]

[g]Rubin MR et al. A 3-dimensional analysis of bone structure using microcomputed tomography. The study included 25 subjects with hypoparathyroidism, with 13 living subjects and 12 cadaver subjects used for age-matched controls.[20]

Burden of Illness

ER visits and hospitalizations[h]

A retrospective chart review of 614 patients with hypoparathyroidism found that **over a 1-year period**[21]:

- **41%** had at least 1 ER visit
  - More ER visits were related to the management of hypoparathyroidism than related comorbidities
- **19.5%** had at least 1 hospitalization
  - The majority of hospitalizations were due to hypoparathyroidism-related comorbidities

Increased risk of comorbidities[i]

Analyses using a Danish Patient Registry found that patients with postsurgical hypoparathyroidism are at a significantly increased risk of developing the following comorbidities[16,22,23]:

COMORBIDITY	HR (95% CI)
Renal insufficiency	3.10 (1.73-5.55)
Nephrolithiasis	4.02 (1.64-9.90)
Seizures	3.82 (2.15-6.79)
Neuropsychiatric disease	2.01 (1.16-3.50)
Infections	1.42 (1.20-1.67)

ER, emergency room; HR, hazard ratio.

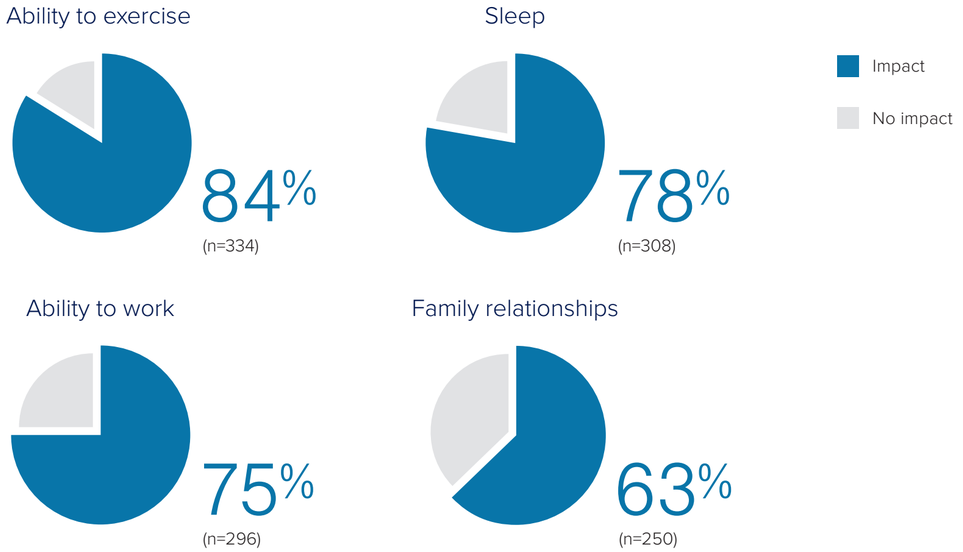
[h]Chen K et al. A retrospective, cross-sectional physician-administered chart review of 614 patients with hypoparathyroidism. Patients were evaluated over a 1-year period. The study evaluated hypoparathyroidism-related healthcare resource utilizations, symptoms, comorbidities, and laboratory values.[21]

[i]Underbjerg L et al (2013, 2014). Two separate case-controlled studies in the same population of 688 patients with chronic postsurgical hypoparathyroidism and 2064 age-matched controls from a Danish National Patient Registry. Patient cases were evaluated to assess CVD, renal disease, psychiatric disease, infections, as well as many other complications.[16,22]

Impact on quality of life[d]

Hypoparathyroidism can have a significant impact on a patient's quality of life. In addition to the physical and emotional symptoms, many patients have reported an interference in their daily activities, employment, and personal relationships.[15]

Results from a global patient and caregiver survey of 397 patients with hypoparathyroidism who self-identified as not adequately controlled with standard therapy and their caregivers[15]:



Management Guidelines for Hypoparathyroidism

The international and European guidelines recommend the following therapeutic goals in order to prevent disease-related complications[8,9]:

GOAL OF THERAPY[8,9]	COMPLICATIONS TO BE PREVENTED[1]
Prevent signs and symptoms of hypocalcemia Maintain serum calcium level slightly below the normal range (ie, no more than 0.5 mg/dL below normal) or in the low normal range	Tetany, seizures, muscle cramps, paresthesia, other neuromuscular complications, fatigue, poor concentration, memory and cognitive function, impaired quality of life, and congestive heart failure (if severe and chronic)
Keep the calcium phosphate product <55 mg^2/dL^2	Ectopic calcifications in the brain, kidney, vascular system, and soft tissues
Avoid hypercalciuria	Kidney stones, nephrocalcinosis, renal dysfunction, and end-stage renal disease
Avoid hypercalcemia	Symptomatic hypercalcemia (weakness, altered mental status, nausea, and abdominal pain) and increased risk of renal calcification
Decrease potential for renal and other extraskeletal calcifications	Renal dysfunction and progression to dialysis or transplantation; central nervous system calcifications and possible dysfunction (eg, seizures, altered mental activity, and movement disorder); and visual loss

Key monitoring parameters based on published literature

ROUTINE ASSESSMENTS[8]	TARGET RANGE[1,4,24]	FREQUENCY[1]
Serum calcium	8.0-9.0 mg/dL	Every 3-6 months — Every 1-2 weeks following adjustments in calcium or vitamin D dose — At least every 3 weeks during pregnancy
Serum phosphate	2.5-4.5 mg/dL	
Calcium phosphate product	<55 mg^2/dL^2	
BUN/creatinine or eGFR	90-120 mL/min/1.73 m^2	
Magnesium	1.7-2.6 mg/dL	
24-hour urine calcium	<300 mg/d	At least once per year — More frequently following adjustments in calcium or vitamin D dose
Vitamin D	>20 ng/mL	

Target-organ evaluations, as clinically indicated[8,10]

- Renal ultrasound or CT scan
- CNS imaging
- Electrocardiogram
- Bone mineral density
- Ophthalmologic examination

BUN, blood urea nitrogen; CNS, central nervous system.

Key Management Strategies Based on Published Literature

INTERVENTION	CONSIDERATIONS
Calcium[8]	— Calcium requirements can vary, ranging from less than 1 g/d up to 9 g/d — Calcium carbonate is most commonly used, but calcium citrate can be considered in certain clinical situations
Active vitamin D[8]	— Typical doses of calcitriol (active vitamin D) are between 0.25 µg/d and 2.00 µg/d — Ergo- or cholecalciferol (parent vitamin D) supplementation may be considered
Thiazide diuretics[8]	— Often used in the presence of hypercalciuria, as they promote calcium retention in the renal tubules — Serum potassium and magnesium should be monitored with diuretic use
Magnesium[10]	— Used if hypomagnesemia is present, which can be due to diuretic or proton pump inhibitor use
Phosphate binders[8]	— Only used in situations where serum phosphate levels are markedly elevated (eg, >6.5 mg/dL) and the calcium-phosphate product is of concern
Dietary changes[8]	— Patients with high serum phosphate levels may need to follow a low-phosphate diet — Patients with high urine calcium levels may need to follow a low-salt diet
Hormone therapy[8]	— Can be considered in patients who are not adequately controlled

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Identifying Patients Who Are Not Adequately Controlled[8]

- Inadequate control of the serum calcium concentration (this could be due to intercurrent illness, compliance, absorption, or intrinsic changes in requirements that are beyond facile correction with calcium and active vitamin D)
- Oral calcium/vitamin D medications required to control the serum calcium or symptoms that exceed 2.5 g of calcium, 1.5 µg of active vitamin D, or 3.0 µg of the 1-α vitamin D analog
- Hypercalciuria, renal stones, nephrocalcinosis, stone risk, or reduced creatinine clearance or eGFR (<60 mL/min)
- Hyperphosphatemia and/or calcium phosphate product that exceeds 55 mg^2/dL^2 (4.4 $mmol^2/L^2$)
- A gastrointestinal tract disorder that is associated with malabsorption
- Reduced quality of life

take a closer look

Evaluating disease control requires careful and frequent monitoring of not only serum calcium, but also serum phosphate, calcium phosphate product, and urinary calcium, in addition to symptoms, quality of life, and comorbidities

Takeda

US-NON-0868v1.0 05/20